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Proteinuria predicting outcome in renal disease: Nondiabetic nephropathies (REIN)

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Proteinuria predicting outcome in renal disease: Nondiabetic nephropathies (REIN). About two thirds of patients on renal replacement therapy irreversibly lose their kidney function because of progressive nephropathies, such as diabetic nephropathy and nondiabetic chronic renal disease. Halting the progression of these patients to end-stage renal disease (ESRD) is instrumental to substantially decrease the need and cost for renal replacement therapy. A large number of experimental studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, even independently of the original etiology. Actually, a variety of insults may result in a common pathway of systemic hypertension, increased glomerular pressure and protein ultrafiltration, glomerular and tubular protein overload, chronic inflammation and, ultimately, scarring. Experimental and clinical data converge to indicate that in chronic renal disease increased protein traffic is nephrotoxic, proteinuria predicts disease progression, and proteinuria reduction is renoprotective. Initial clinical trials, mostly in patients with no or mild proteinuria, failed to demonstrate that ACE inhibition therapy is renoprotective in nondiabetic chronic nephropathies. Consistently, meta-analyses based on data generated by these trials failed to detect a specific, blood pressure–independent, renoprotective effect of ACE inhibition therapy. The Ramipril Efficacy In Nephropathy (REIN) study found that ACE inhibitors, by reducing urinary proteins, may contribute to improve the outcome of nondiabetic renal disease, and reduce the risk of progression to ESRD by about 50%. Cumulative meta-analyses, including the REIN study results, confirmed and extended these findings. Thus, well-designed trials in properly selected and carefully monitored study populations continue to be the best approach to test the efficacy of novel treatments. The meta-analyses may help confirming the consistency of these findings and their generalizability to larger cohorts of patients.

The number of new patients with end-stage renal disease (ESRD) entering kidney replacement programs has progressively increased at an average of 7% per year over the past 10 years [1]. About 1.1 million patients are currently on renal replacement therapy worldwide. This number will exceed two million over the next 10 years; 450,000 of them will be from the United States [2]. Even more people will die of terminal renal failure in countries where renal replacement therapy is not available for the large majority of patients in need. Costs for renal replacement therapy will exceed $1 trillion by 2005. These costs will also exceed the available resources in the richest Western countries [3, 4]. About two thirds of patients on renal replacement therapy irreversibly lose their kidney function because of progressive nephropathies, such as diabetic nephropathy and nondiabetic chronic renal disease. Halting the progression of these patients to ESRD is instrumental in order to substantially decrease the need and cost for renal replacement therapy. Here we will briefly discuss the role of proteinuria in the progression of chronic nephropathies, and of antiproteinuric treatments in preventing progression to ESRD, with a particular focus on the role of ACE inhibition therapy in nondiabetic chronic nephropathies.

Key words: renal protection, ACE inhibition, remission.

MECHANISMS OF RENAL DISEASE PROGRESSION: THE ROLE OF PROTEINURIA

Experimental evidence

A large number of experimental studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, even independently of the original etiology. Actually, a variety of insults may result in a common pathway of systemic hypertension, increased glomerular pressure and protein ultrafiltration, glomerular and tubular protein overload, chronic inflammation and, ultimately, scarring [5–8].

Glomerular hypertension in both diabetic and nondiabetic chronic nephropathies leads to increased glomerular permeability and excessive protein filtration. Ultrafiltered proteins are partly lost in urine (proteinuria), and partly absorbed by endocytosis in the proximal tubules. During periods of heavy proteinuria, the ultrafiltered proteins accumulate in lysosomes in the proximal tubular cells, causing cell disruption and injury (reviewed in [9–12]). Recent data suggest that protein overload may also directly contribute to podocyte injury and eventual glomerulosclerosis [13].

Clinical evidence

A large series of observational studies and clinical trials found a significant correlation between the extent of urinary protein excretion and the rate of GFR decline, as well as of progression to ESRD both in diabetic [14] and nondiabetic [15] chronic nephropathies. A 20-year observational study in a large Caucasian population found that dipstick-positive proteinuria independently predicts risk of ESRD and overall mortality [16]. On the same line, increased urinary albumin excretion predicted increased renal and cardiovascular mortality eight years later in a remote Australian Aborigine community [17]. Recently, a population screening of almost 100,000 people in Japan found that the risk of progression to ESRD over seven-year follow-up was almost entirely restricted to subjects with dipstick proteinuria at study entry, regardless of their renal function to start with [18].

Compelling evidence of a pathogenetic role of proteinuria in the progression of chronic renal disease derives also by data that whenever proteinuria is reduced, regardless of the adopted treatments and of the concomitant changes in blood pressure, disease outcome is also improved (see below).

PROTEINURIA REDUCTION AND NEPHROPROTECTION: EVIDENCE FROM CLINICAL TRIALS AND META-ANALYSES

Randomized, controlled trials have been used for clinical research for more than two centuries, and provide the most unbiased evidence for estimating the efficacy of therapeutic and preventive interventions in human subjects. However, in some circumstances, practical limitations in patient recruitment and study duration may limit the power of the analyses, in particular, when specific subgroups or possible interaction between treatment effects and patient characteristics are considered. The meta-analytic techniques were introduced in 1976 as a quantitative attempt to combine the results of different studies in order to increase the power of the analyses, in particular, when there are several trials addressing a similar clinical issue. Cumulative meta-analyses can be repeated after new trial results are reported, and/or before additional trials are undertaken. On the other hand, heterogeneity in study populations, experimental designs, study treatments, and follow-up period of a considered trial may limit the efficacy of these analyses. An additional, potential bias is also related to the risk of over-representation of positive, published trials versus negative, unpublished studies. Despite these several limitations, the meta-analytic approach has progressively gained popularity over the last years, and nephrologists have started to see in this novel methodology a powerful tool to address some of the issues not definitely addressed by clinical trials. Actually, the role of ACE inhibitor therapy in nondiabetic renal disease has likely been the hottest and controversial issue in clinical nephrology over the last two decades. Here we will briefly consider the specific contribution of clinical trials and meta-analyses of clinical trials in optimizing treatment and prevention of chronic nephropathies, with particular focus on the role of ACE inhibition therapy in nondiabetic renal disease.

ACE inhibition trials in nondiabetic renal disease

Before 1995, several small published [19–22] and unpublished (Brenner BM, personal communication; Toto R, personal communication) randomized trials evaluated the effects of ACE inhibitors in patients with nondiabetic renal disease. None of these, however, clearly demonstrated a specific renoprotective effect of ACE inhibitor therapy. Some studies found that ACE inhibitors slowed GFR decline, but did not reduce the renal events [20], others found some effect on events, but not on GFR [21], and others found no effect at all [19]. Conceivably, these studies were too small and underpowered to test the working hypothesis. This limitation, however, did not apply to the Angiotensin-converting-enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study [23], the largest trial of ACE inhibition in nondiabetic renal disease ever performed. This study, which included 563 patients followed for an average of 3.5 years, found a slower increase in serum creatinine on ACE inhibition therapy than on placebo that did not translate into a reduced risk of progression to ESRD, however. Moreover, the results were flawed by a much more effective blood pressure reduction in the ACE inhibitor group that did not allow establishing whether the beneficial effect on serum creatinine was due to ACE inhibition, per se, or just to a better control of arterial hypertension.

The meta-analyses of ACE inhibition trials

Since 1995 to 1997, three meta-analyses have addressed the issue of ACE inhibition in chronic renal disease [24, 26]. The first two studies [24, 25], however, included a heterogeneous cocktail of patients with diabetic or nondiabetic renal disease, in which the nondiabetic population represented only a minority of the study sample. This likely reflected the fact than most of the studies performed in the early 1990s included patients with diabetic nephropathy, in particular, type 1. Thus, the analyses were primarily aimed to evaluate the effects of ACE inhibitors in chronic nephropathies regardless of the underlying etiology. Due to the limited power, subgroup analyses in nondiabetic patients could just evaluate whether the trends observed in these patients reflected those more consistently demonstrated in diabetics. Altogether, these studies found a 40% risk reduction for ESRD or doubling serum creatinine on ACE inhibitor therapy compared to

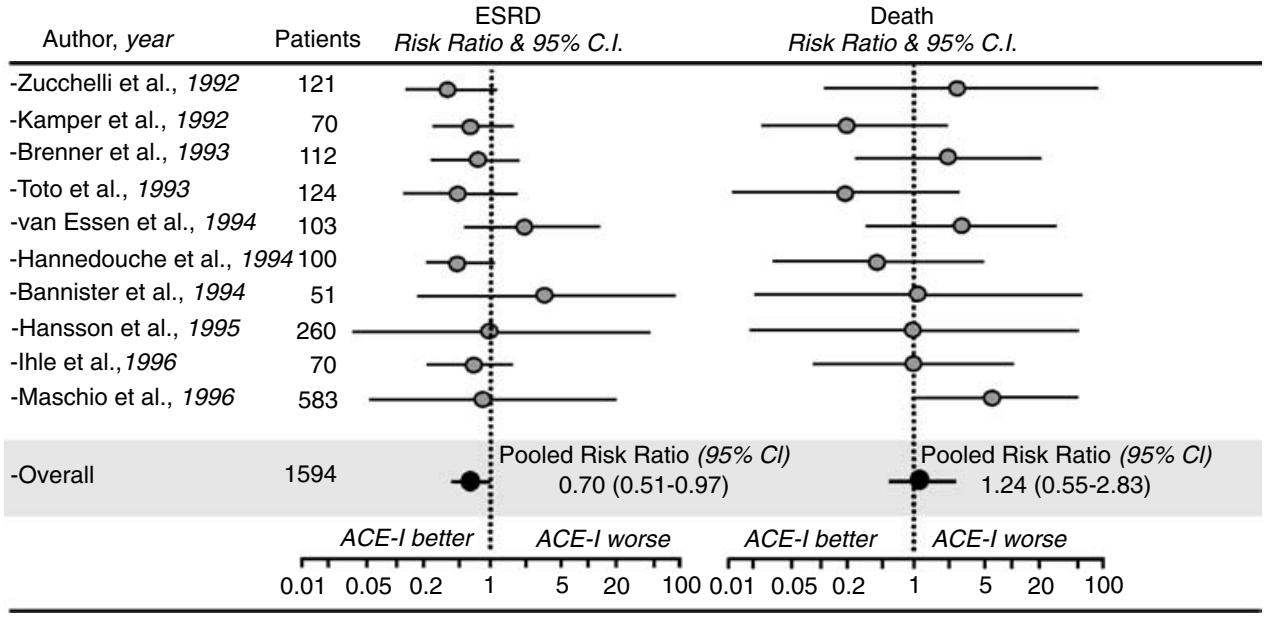

Fig. 1. Risk ratios (and 95% confident intervals) of ESRD or death in a meta-analysis of 11 trials of 1594 patients with nondiabetic renal disease randomized to ACE inhibitor therapy or placebo. Modified from [26].

placebo in both diabetic and nondiabetic patients [24, 25]. In 1997, however, the availability of a large amount of data derived by the AIPRI trial provided for the first time enough power to perform a meta-analysis specifically focused on chronic nondiabetic nephropathies [26]. The results, however, were discouraging. Although the study found a marginal benefit on the risk of ESRD (Fig. 1), the hypothesis of a specific renoprotective effect of ACE inhibitors remained unproven because of the significantly better blood pressure control in subjects on ACE inhibitor therapy. Moreover, the overall mortality was not improved by ACE inhibition, largely because the excess mortality observed on benazepril treatment in the AIPRI study [23] counterbalanced the trend to a lower mortality on ACE inhibition therapy observed in the other trials (Fig. 1). Why renal outcome data differed from those in diabetic renal disease is unclear. A possible explanation is that the large majority of patients considered in this meta-analysis had mild or no proteinuria. In these cases, the GFR decline is slow, and the renal events (ESRD disease or doubling serum creatinine) are relatively few. This unavoidably decreases the power of both slope-based and event-based analyses. Another important point is that ACE inhibitors are maximally effective in patients with most severe proteinuria, but have only marginal effects in those with subclinical or no proteinuria, such as those with adult polycystic kidney disease, or chronic tubulointerstitial nephropathies. Thus, the results were substantially inconclusive because the meta-analysis could not prove, or reject, the working hypothesis. A different approach was needed.

The REIN study

To increase the power of the analyses, the investigators of the Ramipril Efficacy In Nephropathy (REIN) study decided to test the renoprotective effect of ACE inhibition therapy in a population of patients predicted to rapidly progress because of a persistently (for six months or more) increased (1 g per day or more) urinary protein excretion rate [27]. Serial measurements of the GFR by the iohexol plasma clearance technique [28] allowed also for powerful slope-based analyses of GFR decline. After stratification for baseline proteinuria 1 to 3 g/day (Stratum 1) or ≥3 g/day (Stratum 2), patients were randomized to ramipril or placebo plus other non-renin-angiotensin-system–inhibiting agents targeted at achieving and maintaining a diastolic blood pressure of 90 mm Hg or less in both treatment groups. This prevented the confounding effect of more blood pressure reduction in the ACE inhibition arm that flawed the analyses of previous studies [23]. The interim analyses of the study found a two- to three-fold faster GFR decline in patients with baseline proteinuria >3 g/24 hours than in those with less proteinuria, a finding that confirmed and extended the evidence of a specific pathogenetic role of proteinuria in the progression of chronic nephropathies [27, 29, 30] (Fig. 2). Moreover, in patients with proteinuria >3 g/day, ramipril halved the rate of GFR decline (Fig. 2), an effect that induced the Ethical Committee to prematurely stop Stratum 2 for efficacy reasons and to put all patients on ramipril therapy regardless of the original randomization. These patients entered the REIN follow-up study [29]. In the meantime, final analyses of Stratum 2 (Core

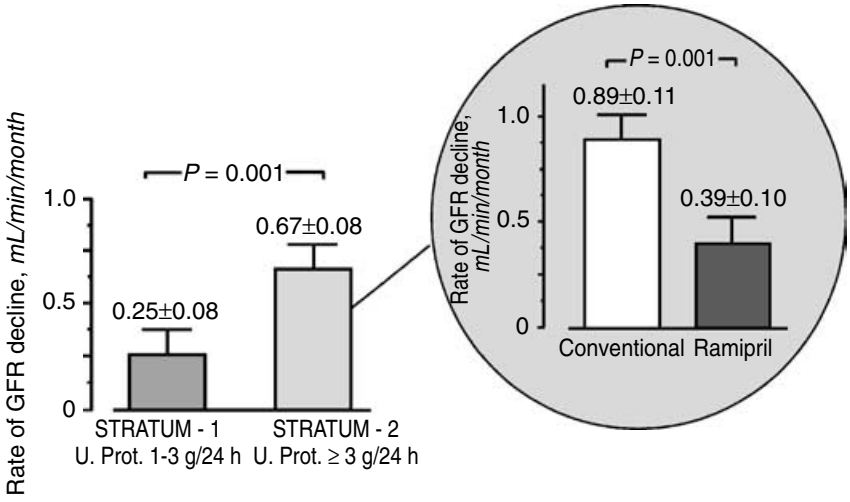

Fig. 2. Rate of GFR decline at interim analysis of 177 patients with nondiabetic chronic nephropathies included in the REIN study, according to baseline proteinuria and treatment randomization.

Study) found also a halved risk of doubling serum creatinine or ESRD on ACE inhibition compared to placebo [27]. A similar benefit on renal events was subsequently described also in Stratum 1 patients [30]. Finding that in patients on ramipril therapy the improved outcome was associated with more proteinuria reduction, but comparable blood pressure versus controls reinforced the concept that the renoprotection conferred by ACE inhibition was largely mediated by the effects on urinary proteins [27]. This was also consistent with finding that at multivariate analyses ACEi-induced reduction in urinary proteins was the strongest time-dependent covariate that predicted a lower rate of GFR decline and a slower progression to ESRD. Finding that the rate of GFR decline was correlated negatively with proteinuria reduction, and positively with residual proteinuria, provided further evidence of the role of protein traffic in the progression of the disease [31]. Of interest, proteinuria reduction was more consistent in patients with more proteinuria to start with. Thus, patients with more severe disease were also those who gained the most from ACE inhibition therapy both in terms of more proteinuria reduction and of slower progression.

After about 36 months of treatment with ramipril, no further patients progressed to the point of requiring dialysis, whereas patients switched from conventional therapy to ramipril continued to develop end-stage renal disease [32]. During the Core Study, ramipril therapy was associated with a 50% reduction in the risk of outcome events (ESRD or doubling of serum creatinine), whereas during the follow-up phase, patients originally randomized to ramipril had, at most, a three-fold reduction in the risk of reaching end points. Thus, the renoprotective effect of ACE inhibition was clearly time-dependent, and in the long-term resulted in a stabilization of the disease, This remarkable outcome should be considered in the light of the fact that these patients all had >3 g/day of proteinuria before the study and were, therefore, expected to develop rapid decline in GFR [33].

Of interest, post-hoc analyses found a comparable outcome in males and females that challenged previous evidence of a gender effect resulting in a fasting progression of chronic nephropathies in males. Actually, the REIN study found that the comparable outcomes in the two genders were the result of a faster progression on placebo, and of a better response to ACE inhibitor therapy of females compared to males. These opposite trends were specifically related to gender, since they persisted even after adjustments for a series of potential confounders, such as blood pressure control and dietary sodium and protein intakes [34].

The cumulative meta-analyses including the REIN study results

The Angiotensin-converting-enzyme Inhibition and Progression of Renal Disease (AIPRD) study, a cumulative meta-analysis of 11 trials including the REIN trail, confirmed that proteinuria is a strong risk factor for progression of chronic renal disease that can be effectively modified by ACE inhibitor therapy [35]. Of interest, the REIN study [27] and the AIPRD meta-analysis [36] consistently found that the risk reduction for ESRD achieved by ACE inhibitor therapy versus placebo increased for increasing levels of baseline proteinuria (Fig. 3). In other words, the meta-analysis confirmed previous evidence from the REIN study that patients with more severe renal disease are those who benefit the most from ACE inhibitor therapy. These findings were confirmed and further extended by a pooled analysis of 2387 patients with nondiabetic renal disease showing a strong relationship between early changes in urinary proteins achieved by different renoprotective treatments (ACE inhibition, blood pressure reduction, or low protein diet) and subsequent disease outcome [33] (Fig. 4). Indeed, in the 1710 patients in whom proteinuria was reduced by treatment,

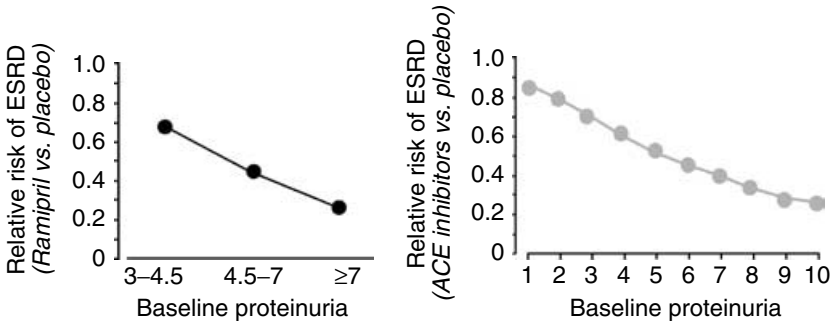

Fig. 3. Relative risks of ESRD on ACE inhibition therapy or placebo according to different levels of baseline proteinuria in patients with nondiabetic chronic nephropathies enrolled in the REIN Stratum 2 study (left panel) or in the AIPRD meta-analysis (right panel).

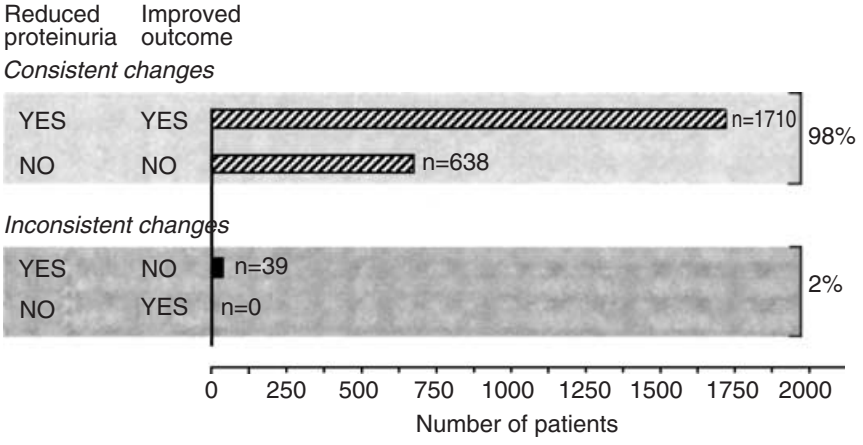

Fig. 4. Renal outcomes according to changes in urinary proteins in a pooled analysis of 2387 patients with nondiabetic chronic nephropathies included in 11 randomized trials of different renoprotective treatments. Modified from [33].

the outcome was also significantly improved, whereas in the 638 patients in whom proteinuria was not reduced, the outcome was not appreciably affected. Even more important, in no case was there a worsening in proteinuria that was subsequently associated with an improved outcome. Thus, in 98% of the patients, changes in proteinuria and outcome were consistent with a pathogenetic role of proteinuria in disease progression, and with a nephroprotective effect of proteinuria reduction (Fig. 4). In only 39 patients was no improvement in disease outcome detected, despite a reduction in urinary proteins. These patients, however, were included into two small studies with only one-year follow-up that were too underpowered to detect any appreciable treatment effect on disease outcome.

An additional cumulative meta-analysis of 1860 nondiabetic patients found that in those with a basal urine protein excretion more than 2.0 g/day, systolic blood pressure of 110 to 129 mm Hg was associated with the lowest risk for kidney disease progression [37]. In those with less proteinuria, no relationship was found between achieved blood pressure control and outcome. Again, these findings confirmed and extended evidence from previous trials, such as MDRD [38], REIN [27], and AASK [39] studies, that the benefit of blood pressure reduction on disease outcome strongly depends on the extent of proteinuria, the outcome being substantially improved in patients with more proteinuria, but only marginally affected in those with subclinical or no proteinuria. A novel finding of this meta-analysis, however, was that systolic blood pressures less than 110 mm Hg were associated with an increased risk of doubling of serum creatinine or ESRD [37], a phenomenon that to some extent recalled the "J effect" on cardiovascular events attributed in some studies to a too intensive blood pressure reduction. A reduced kidney perfusion was suggested to explain the worsening renal function in patients with more blood pressure reduction. The authors, however, acknowledged that their analyses could not exclude the possibility of a reverse causation. In other words, the meta-analysis could not establish whether the findings reflected a specific pathogenetic role for too low blood pressure, per se, or merely the common association between low blood pressure and diseases such as focal segmental glomerulosclerosis and some cases of idiopathic membranous nephropathy that are characterized by heavy proteinuria and poor outcome. Thus, whether intensified blood pressure control is protective or detrimental for the kidney can be assessed only by an ad hoc clinical trial.

A meta-analysis from the same group [40] also found that, after adjusting for potential confounders such as diet, blood pressure, or lipid profile, renal disease progression was comparable in women and men. These findings challenged previous evidence of a gender

effect on disease progression from studies that, however, did not consider these confounders [41], and confirmed and extended evidence from the REIN study that progression of nondiabetic renal disease was comparable in women and men [34]. The possibility of an interaction between ACEi therapy and gender arisen by the REIN data, however, was not formally explored in this meta-analysis.

CONCLUSION

Experimental and clinical data converge to indicate that in chronic renal disease increased protein traffic is nephrotoxic, proteinuria predicts disease progression, and proteinuria reduction is renoprotective. Initial clinical trials failed to demonstrate that ACE inhibition therapy is renoprotective in nondiabetic chronic nephropathies. Consistently, meta-analyses based on data generated by these trials failed to detect a specific, blood pressure–independent, renoprotective effect of ACE inhibition therapy. The REIN study found that ACE inhibitors, by reducing urinary proteins, may contribute to improve the outcome of nondiabetic renal disease. Cumulative meta-analyses including the REIN study results confirmed and extended these findings.

Thus, well-designed trials in properly selected and carefully monitored study populations continue to be the best approach to test the efficacy of novel treatments. The meta-analyses may help confirming the consistency of these findings and their generalizability to larger cohorts of patients.

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